REMARKS

Currently pending claims

Claims 5, 8, 11, and 13-21 are currently pending in the application.

Rejections under 35 U.S.C. § 103

Claims 5, 8, 11, 13, and 15-20 stand are rejected under 35 U.S.C. § 103 as being unpatentable over Avidano et al. in view of Lezdey (U.S. Patent No. 6,174,859). In addition, claims 14, 20 and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. in view of Lezdey et al., as applied to claims 5, 8, 11 and 13 above and further in view of Brake et al. (U.S. Patent No 4,752,576).

An obviousness inquiry is controlled by the factors articulated by the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of nonobviousness. In addition, a long line of Federal Circuit decisions has established that a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person of ordinary skill in the art provides some motivation or suggestion to combine the prior art teachings (the "teaching, suggestion, or motivation" or "TSM" test). While the Supreme Court has recently rejected a rigid application of the TSM test, it stated that the Graham Deere factors still control an obviousness inquiry. See KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. at 1727. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." KSR, 127 S. Ct at 1731. The Court specifically acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. Id. As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. Id.

Applying these principles, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because **(I)** the references cited do not teach or suggest all limitations of the currently pending claims, **(II)** there is no reasonable expectation of success, **(III)** the Examiner has based obviousness on improper hindsight, and **(IV)** the references teach away from the present invention.

I. References do not teach or suggest all the claim limitations.

Applicants submit that Avidano et al. and Lezdey et al. do not teach or suggest all the claim limitations of the present invention. Moreover, the Examiner has failed to apply the proper legal standard for comparing the present invention to the cited references.

A. Legal Standard for comparing Prior Art and Claimed Invention.

As per M.P.E.P §2141.02 I, in "determining the differences between the prior art and the claims, the question under **35 U.S.C. 103** is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)." [Emphasis in original] The U.S. Court of Appeals for the Federal Circuit regularly applies the "as a whole" legal standard for comparing the prior art and the claimed invention. (see Freedman Seating Co. v. American Seating Co., 420 F.3d 1350 (Fed. Cir. 2005); Princeton Biochemicals, Inc. v. Beckman Coulter, Inc., 411 F.3d 1332 (Fed. Cir. 2005); Ruiz v. A.B. Chance Co., 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004)). In addition, distilling "an invention down to the 'gist' or 'thrust' of an invention disregards the requirement of analyzing the subject matter 'as a whole.' W.L. Gore & Associates, Inc. v. Garlock, Inc. 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)" (see M.P.E.P §2141.02 II). Thus, an Examiner is legally required to consider a claimed invention "as a whole" and must take into account all the limitations recited in the claimed invention. To do otherwise disregards the statutory requirement that the invention be viewed "as a whole."

B. Application of the Legal Standard

1. Without signficant ototoxicity

Currently pending claim 13 recites a method for "treating an individual having otitis media and a perforated tympanic membrane ... wherein the otitis media is treated without significant ototoxicity." [Emphasis added] According to the present invention, ototoxicity involves the "tendency of certain substances to cause functional impairment and cellular damage to tissues of the external, middle, and especially the inner ear." (specification page 11, paragraph 37). Examples 2 and 3 describe experiments performed in the well-established chinchilla model for otitis media, in which middle ear infections were induced and subsequently treated with alpha one-antitrypsin (AAT), or AAT and ilomastat. These examples also demonstrate that the auditory thresholds do not change in AAT-treated and control-treated ears. Therefore, the present specification provides evidence that treatment of otitis media with AAT exhibits "no significant ototoxicity" as recited in currently pending claim 13.

Unlike the present invention, Applicants reiterate that neither Avidano et al. nor Lezdey et al. teach or suggest the "without significant ototoxicity" limitation and that the Examiner has not established this to the contrary. As previously argued by Applicants, Avidano et al. discloses results for ***in vitro*** protease activity assays conducted on specimens taken from human patients in which ilomostat and alpha 1-antitypsin (AAT) were added to the experimental samples. The assay measures protease activity in the sample but says nothing about the ototoxicity of ilomostat and AAT. In addition, as Applicants have previously argued, Lezdey et al. likewise provides no information about the ototoxicity of agents for the treatment of otitis media. The reference is limited to two examples (Examples 2 and 6) that refer to an otopical formulation. Example 2 discloses a mixture containing AAT, which was "dosed into the ear of a patient with swimmer's ear three times a day" and concludes that pain was reduced with the initial dose. This Example provides no information on ototoxicity of AAT because all it reports is pain reduction. Example 6 is purely prophetic and states that a mixture of AAT "is prepared", "can be adminstered into an infected ear", and pain and inflammation "will be reduced immediately." [Emphasis added] There is no indication that the mixture even achieves what the patentee claims and even

assuming *arguendo* that it did, a reduction in pain and inflammation says nothing about ototoxicity.

In summary, a decrease in protease activity observed in an ***in vitro*** assay combined with a reported reduction of pain in a subject with swimmer's ear neither teaches or suggests the treatment of otitis media "without significant ototoxicity" as recited in the currently pending claims.

2. Perforated tympanic membrane

Currently pending claim 13 recites a method of "treating an individual having otitis media and a perforated tympanic membrane" [Emphasis added]. The instant specification provides that a perforation may be deliberate (e.g. insertion or replacement of a post-tympanostomy tube) or non-deliberate (e.g. occuring over the natural course of otitis media) (see page 5, paragraph 16). It is well-established in the art that a perforated tympanic membrane contributes to ototoxicity (see page S57, 2nd paragraph of right column in Roland et al. Otolaryngol. Head Neck Surg. 130:S57-S78 (2004); and page S81 under Conclusions section of Matz et al. Otolaryngol. Head Neck Surg. 130:S79-S82 (2004) (both already of record)). Applicants discovery concerns the unexpected ability of alpha 1-antitrypsin to successfully treat otitis media "without significant ototoxicity" (see Examples 2 and 3) including ototoxicity associated with a perforated tympanic membrane. As discussed above, neither Avidano et al. nor Lezdey et al. disclose or suggest the treatment of otitis media "without significant toxicity", or for that matter the treatment of otitis media "without significant toxicity" associated with a perforated tympanic membrane.

In summary, a decrease in protease activity observed in an ***in vitro*** assay combined with a reported reduction of pain in a subject with swimmer's ear neither teaches or suggests the treatment of otitis media "without significant ototoxicity" associated with a perforated tympanic membrane as recited in the currently pending claims.

C. The Examiner has not applied the proper legal standard.

Applicants respectfully submit that the Examiner has not applied the proper legal standard for comparing the presently claimed invention to Avidano et al. and Lezdey et al. Although required to consider the invention "as a whole", the Examiner has not done so, namely by disregarding the ototoxicity and perforated tympanic membrane limitations. The Examiner has asserted that it would have been obvious to

> employ the teaching of Avidano et al. to a patient (vivo) suffering from otitis media ... by administering effective amount of alpha one-antitrypsin without significant ototoxicity because Avidano et al. obtained statistically significant decrease in protease activity against Pseudomonas in the sample collected from human who actually had otitis media and because the effective therapeutic amount of alpha one-antitrypsin for the treatment of ear infection cause by pseudomonas is well known by Lezdey et al. [Emphasis added] (page 5 of the July 9, 2007 Office Action)

Applicants respectfully submit that without explanation, the Examiner has improperly made the leap from the disclosure of pain reduction in Example 2 of Lezdey et al. to the Applicants' discovery of the treatment of otitis media "without significant ototoxicity" associated with a perforated tympanic membrane. As argued above, a decrease in protease activity observed in an ***in vitro*** assay combined with a reported reduction of pain in a subject with swimmer's ear does not teach or suggest the treatment of otitis media "without significant ototoxicity" associated with a perforated tympanic membrane as recited in the currently pending claims. The Examiner has advanced this unsupported conclusion before. As previously asserted by the Applicants, the Examiner failed to address the "without ototoxicity" limitation in the December 15, 2006 Office Action (page 6 of the March 15, 2007 Office Action). Thus, despite two opportunities to address an important limitation of the currrently pending claims that was called to the Examiner's attention by the Applicants, the Examiner has not done so.

As discussed above, the Examiner's omission is impermissible under the statutory requirements of 35 U.S.C. § 103, the legal standard established by the U.S. Court of Appeals for Federal Circuit, and the rules of the M.P.E.P.. In disregarding the "without ototoxicity" associated with a perforated tympanic membrane limitation, the Examiner has not considered the Applicants' presently claimed invention "as a whole." Furthermore, Applicants submit that the

Examiner has impermissibly distilled Applicants' invention to a method of treating a patient with the protease inhibitors disclosed in Avidano et al. and chosen to ignore the uncertainty and potential ototoxicity associated with actual treatment. Accordingly, Applicants submit that the rejection should be withdrawn.

In summary, Applicants submit that the references cited by the Examiner do not teach or suggest the "without significant ototoxicity" associated with a perforated tympanic membrane limitation of claim 13. As such, upon application of the proper legal standard for comparing the currently pending claims to Avidano et al. and Lezdey et al., the Examiner must find that the currently claimed invention "as a whole" is non-obvious over the references cited. Therefore, Applicants submit that the Examiner has not established a *prima facie* case of obviousness and Applicants request the withdrawal of the rejection of claim 13 and any claim depending therefrom.

II. Avidano and Lezdey provide no reasonable expectation of success.

Applicants respectfully submit that the skilled artisan would not have a reasonable expectation of success in practicing the invention *as claimed* based on the teachings of the references. The Examiner's consideration of this requirement for a *prima facie* case of obviousness is as follows.

> Absent any evidence to the contrary, there would be a reasonable expectation of successfully treating an individual having otitis media and a perforated tympanic membrane with alpha one-antitrypsin well known by Avidano et al. having significant antiprotease activity in human otitis media sample. [pages 5-6 of the December 15, 2006 Final Office Action and pages 5-6 of the July 9, 2007 Office Action]

As a preliminary matter, Applicants respectfully submit that the Examiner has once again erred in failing to consider the "without significant ototoxicity" limitation recited in the currently pending claims. In addition, Applicants submit that the Examiner's mere statement above does not establish that a combination of Avidano et al. and Lezdey et al. provides a reasonable expectation of success in practicing the Applicants' claimed invention. Applicants have, in fact, already provided "evidence to the contrary" that the Examiner seems to require. As previously

argued by Applicants, it is clear that those of ordinary skill in the art view ototoxicity as an area of critical concern in the development of therapeutic agents for otitis media. For example, as Applicants established in their March 15, 2007 Response, Roland et al. and Matz et al. demonstrate the well-known toxicity of varous antibiotics that have been used for the ototopical treatment (page 5-6 of the March 15, 2007 Response). In addition, prior to Applicants' discovery, it could not be predicted whether AAT would prove sufficiently nonototoxic as to permit effective topical administration in the setting of a perforated tympanic membrane. Indeed, with agents drawn from a wide range of chemical classes having already, in some cases tragically, proven ototoxic,[1] the art instead clearly counsels caution in attempting topical therapy with novel agents. Given the clear evidence of such caution Roland et al. and Matz et al., the cited art could not have provided a reasonable expectation that an effective, yet nonototoxic, dose of AAT could found that would permit successful treatment of otitis media in the setting of perforated tympanic membrane in the absence of significant ototoxicity.

Applicants submit, therefore, that the Examiner has not established a *prima facie* case of obviousness *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art."). With failure of the *prima facie* case, the burden of production has not properly been shifted to applicants, and applicants are entitled, without more, to their claims. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

Applicants respectfully submit that currently pending claim 13 and all claims depending therefrom are non-obvious over the art of record, and that the rejection is in error and should be withdrawn.

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[1] See Roland *et al.*, Table 1.

III. The Examiner has based obviousness on improper hindsight.

Applicants respectfully submit that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning. As discussed above, the references cited by the Examiner do not teach or suggest the treatment of otitis media "without significant toxicity", or for that matter the treatment of otitis media "without significant toxicity" associated with a perforated tympanic membrane. In addition, given the ototoxcity problem known in the art, there is no reasonable expectation that a combination of Avidano et al. and Lezdey et al. would succeed because it could not predicted whether AAT would prove sufficiently nonototoxic as to permit effective topical administration in the setting of a perforated tympanic membrane. Indeed, there is no doubt that the Examiner has used the disclosure of the present application to pick and choose selected portions of Avidano et al., which were then combined with Lezdey et al. in an attempt to recreate the claimed invention. Applicants respectfully submit that the Examiner's conclusion is based upon an improper hindsight reconstruction of the claimed invention, which, instead of looking at the prior art as a whole, picks and chooses teachings that appears to support a finding of obviousness, while completely disregarding others.

IV. Lezdey et al. teaches away from the present invention.

As the Examiner is aware, a "prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)" (M.P.E.P. §2141.02 VI). As previously asserted by the Applicants, Lezdey et al. actually teaches away from the administration of AAT to patients with a perforated tympanic membrane because Lezdey et al. teaches combining the AAT with antibiotics which are known to be ototoxic. For example, the reference states its compositions are medicametous forms "particularly suitable for ... otolaryngologic application." (Col. 2, lines 28-31) In addition, it is stated that the medicamentous forms may contain "antibiotics such as bacitracin, ... [neomycin], tetracycline, or choramphenicol". (Col. 2 line 64 to Col. 3 line 1). Each of these

antibiotics is listed in Table I of Roland et al. of record, which describes various reports of ototoxicity from antibiotic drops administered to animals.

Thus, Lezdey et al. clearly teaches away from the "without significant ototoxicity" limitation recited in the currently pending claims. Accordingly, Applicants submit it cannot form the basis of an obviousness rejection.

V. Avidano et al, Lezdey et al., and Brake et al.

Claims 14, 20 and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Avidano et al., of record in view of Lezdey et al., as applied to claims 5, 8, 11 and 13 above and further in view of Brake et al. (U.S. Patent No 4,752,576).

Applicants traverse the rejection and respectfully submit that based upon the Applicants' previous arguments, the Examiner has failed to establish a *prima facie* case of obviousness based on Avidano et al. and Lezdey et al.. Furthermore, the citation of Brake et al. does not cure the deficiencies of these primary references. Accordingly, a combination of these three references does not render claims 14, 20, and 21 obvious.

Applicants respectfully submit that the claims as now pending are nonobvious over the references cited by the Examiner, and that the rejection is in error and should be withdrawn.

CONCLUSION

Applicants submit that the present application is in condition for allowance, and respectfully request the same. If the Examiner believes that any matters remain outstanding prior to passing this case to issue, however, applicants respectfully request that the Examiner call the undersigned attorney, newly of record, for a telephonic interview.

Although no fees are believed to be due at this time, please charge any fees that might become applicable, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39042-0014**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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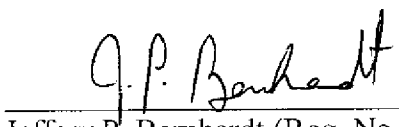
Date: January 8, 2008



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